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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/395,038	09/13/99	TRINCHIERI G	WST85USA

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1646	9

DATE MAILED: 03/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/395,038	Trinchieri et al.	
	Examiner	Art Unit	
	Sarada C Prasad	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *16-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-15,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Detailed Action

1. Receipt of Applicants' response to election/restriction of Group I species (a) (claims 1-15) with traverse, in Paper No. 8 (1/8/01), is acknowledged.

The traversal is on the grounds that the claims of Group I are methods for enhancing the adjuvant effect of IL-12 by co-administering IL-12, a vaccine antigen, and a nitric oxide inhibiting and/or neutralizing agent. As asserted by the Applicants, claim 40 is directed to an adjuvant composition containing IL-12 and a nitric oxide inhibiting and/or neutralizing agent, while claim 41 is directed to a vaccine composition containing IL-12, a vaccine antigen, and a nitric oxide inhibiting or neutralizing agent. The Applicants' arguments in favor of combining claims 1-15 and 40, 41 for examination purposes are persuasive. Therefore the Examiner has decided to include claims 1-15 of Group I species (a) and claims 40, 41 for examination.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claim 40 is rejected under 35 USC § 101 the claimed invention is directed to non-statutory subject matter.

Claim 40 recites "An adjuvant composition suitable for use with a vaccine..." without setting forth any steps involved in the process, resulting in an improper definition of a process, i.e., resulting in a claim which is not a proper process claim under 35 USC § 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112-second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-15, 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3a. Claim 1, 40, 41 are rejected for the claim language "nitric oxide inhibiting and/or neutralizing agent". The vague and indefinite nature of the phrase 'and/or' when referencing nitric oxide inhibiting and/or neutralizing agent is confusing because it is not clear exactly if both reagents are included or only one of the components is included at any given instance. Applicants must clearly recite exact steps in claims.

Claims 2-15 are rejected insofar as they depend on claim 1.

3b. Claim 40 is rejected because claim 40 provides for the use of adjuvant composition suitable for use with a vaccine antigen, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. This rejection may be obviated by reciting "A method of preparing an adjuvant composition comprising a vaccine antigen comprising .....".

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-15, and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,723,127 (1998), in view of Fecho et al. (1994).

U.S. Patent No. 5,723,127 (1998) (by the same inventors, supplied as reference AC of IDS) teaches a method to employ IL-12 as an effective adjuvant in vaccine compositions and methods of making the compositions. Their disclosure provided a method of making pharmaceutical compositions useful as a vaccine comprising an antigen from a pathogenic microorganism combined with an effective adjuvanting amount of IL-12. U.S. Patent No. 5,723,127 also taught that these adjuvanted vaccines are capable of increasing the vaccinated host's cell-mediated immune response to provide an increased and protective immune response

to the pathogen (column 2, para 4, lines 1-7). It is well known in the art that the desirable therapeutic effects of IL-12 can be accompanied by dose and schedule dependent toxicities. Therefore, there is a compelling need to achieve low, non-toxic doses of IL-12 that provide adjuvanting effect. However, U.S. Patent No. 5,723,127 did not teach co-administering an effective amount of a nitric oxide inhibiting and/or neutralizing agent in order to further enhance the immunostimulatiory effect of IL-12.

Fecho et al. (1994) (supplied reference BU of IDS) disclose that macrophage(adherent cell)-derived nitric oxide is involved in the depressed concanavalin A responsiveness, namely, proliferative and immune responses, of splenic lymphocytes. Fecho et al (1994) also pointed out that inclusion of nitric oxide synthase inhibitors such as L-NAME (N-Monomethyl –L-Arginine) restored con A responsiveness thereby concluding that the observed immunosuppression (low levels of immunostimulation) is due to the existing levels of nitric oxide.

Therefore, it would have been obvious to one of ordinary skill in the art to conclude that removal of nitric oxide produced by the adherent cells from the vicinity of IL-12 action in order to obtain the desired immunostimulatory and adjuvanting effect of IL-12, in particular, in enhancing cell-mediated immunity making claims 1-2, 4-11, 40-41 obvious. The motivation is provided by the diverse (opposing) effects of administration of higher doses of IL-12 and the need to further enhance immunostimulatory activity of IL-12 at lower doses.

Use of inhibitors of iNOS such as L-NMMA (Fecho et al. page 5847, column 2, lines 15-end) makes it obvious to use other compounds with comparable structure like L-NAME or L-NAA making instant claims 2, 7-11 obvious.

Co-administration of IL-12, vaccine antigen, and NO inhibitors would be obvious to one of ordinary skill in the art while screening the immunostimulatory effect of IL-12 to any given vaccine antigen in animal model systems, thus making claims 4-6 obvious. Once elimination of NO is the set goal, then inhibition of synthesis, increased degradation or inactivation are the various means of achieving the same goal. Therefore, it would have been obvious to one of skill in the art to use NO scavengers (instant claims 2-3, and 12-13).

U.S. Patent No. 5,723,127 (1998) teaches use of antigens from several pathogenic bacteria, viruses as vaccine antigens in combination with IL-12 and NO inhibiting substances in attempts to stimulate antibodies to the antigens causing the various pathogenic infections (claims 1-8, column 27, 28). It would have been obvious to one of ordinary skill in the art to have replaced bacterial/viral/fungal antigens with tumor cell surface antigens because it would be a useful application in cancer therapy, making instant claim 14-15 obvious.

4b. Pertinent Prior art of record: Liew et al. (Sept. 29, 1997), Cytokines and nitric oxide as effector molecules against parasitic infections (Form PTO 892).

Conclusion

5. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday – Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
March 9, 2001

Prema Mertz
PREMA MERTZ
PRIMARY EXAMINER